REMARKS

The above amendments to the above-captioned application along with the following remarks are being submitted as a full and complete response to the Official Action dated September 25, 2002, the period for response to which will expire on December 25, 2002.

In view of the above amendments and the following remarks, the Examiner is respectfully requested to give due reconsideration to this application, to indicate the allowability of the claims, and to pass this case to issue.

Claims 1-4 and 30-37 are under consideration in this application. Claims 1, 30 and 34 are being amended, as set forth above and in the attached marked-up presentation of the claim amendments, in order to more particularly define and distinctly claim applicants' invention. Applicants hereby submit that no new matter is being introduced into the application through the submission of this response.

Prior Art Rejection

Claims 1-4 and 30-37 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Vijg et al. (WO 98/06872; US 6,007,231, hereinafter "Vijg") in view of Xu et al. (Genomics 1998 Vol. 47, pp. 171-179) and further in view of Harris (Genome Research 1997 Vol 7, pp754-762, hereinafter "Harris"). The rejection has been carefully considered, but is most respectfully traversed.

The primer design system according to the present invention, as now recited in claim 1, comprises means for selecting at least one genomic DNA nucleotide sequence from a database including a plurality of DNA nucleotide sequences; means for predicting a plurality of exons of said selected DNA nucleotide and for storing positions of the predicted exons; means for using each of the predicted exons as a template to design one corresponding primer pair for each of the predicted exons and for designing corresponding primer pairs for the predicted exons simultaneously; and means for automatically collating said plurality of primer pairs with said predicted exons and the DNA nucleotide sequence.

The invention, as now recited in claim 30, also is directed to a method for designing primers comprising the steps of: selecting at least one DNA nucleotide sequence from a genomic DNA database; predicting a plurality of exons of said selected DNA nucleotide; using each of the predicted exons as a template to design one corresponding primer pair for each of the predicted exons and for designing corresponding primer pairs for the predicted exons simultaneously; and automatically collating said plurality of primer pairs with said predicted exons and the DNA nucleotide sequence.

The invention, as now recited in claim 34, is further directed a primer design system comprising: means for selecting at least one genomic DNA nucleotide sequence from a database including a plurality of DNA nucleotide sequences; means for predicting a plurality of exons of said selected DNA nucleotide and for storing positions of the predicted exons; means for using each of the predicted exons as a template to design one corresponding primer pair for each of the predicted exons and for designing corresponding primer pairs for the predicted exons

simultaneously; and means for evaluating specificity of each designed primer or each designed primer pair.

The feature of the invention is a primer design system and method in which a plurality of exons of selected DNA nucleotide from genomic DNAs are predicted by exon prediction program, a plurality of primer pairs are designed using each of the predicted exons as a template simultaneously, and the plurality of primer pairs are collated with the predicted exons and the DNA nucleotide sequences. The primer pairs are designed simultaneously using each of a plurality of exons as a template. Therefore, the invention supports high-throughput screening (page 37, lines 4-8). For example, during the analysis of differences in gene levels occurring between normal individuals and patients afflicted with a certain disease (such as cancer), genomic DNAs extracted from the cells of various individuals are used as templates to carry out PCR using a plurality of primers for mutually different exons, and the exons which are believed to be related to the disease can be determined based on types of primers having differences in nucleotide sequences and the length or presence/absence of amplified fragments (page 5, lines 13-22).

First, Applicants respectfully contend that neither Vijg nor Xu teaches or suggests "using each of the predicted exons as a template to ***design*** one corresponding primer pair for each of the predicted exons and for designing corresponding primer pairs for the predicted exons **simultaneously**".

In contrast, Vijg only ***amplifies*** the exons simultaneously, but designs the primers based upon one target sequence, such as an exon, at a time (i.e., **one by one**). Vijg teaches a method in which many different exons are amplified simultaneously in the same reaction. In this method, group of exons are amplified by long-distance PCR, and then large numbers of individual target sequences can be amplified simultaneously in the same reaction vessel under a single set of experimental conditions (page 5, third paragraph; page 6, first paragraph).

Xu is replied upon by the Examiner in this regard; however, it fails to compensate for Vijg's deficiencies. Xu teaches an experimental protocol which is able to identify exon boundaries in a ***cDNA*** (which is composed only by exons) with the ExonPCR algorithm so as to predict a plurality of exons. In the present invention, exons are predicted in at least one ***genomic DNA*** (consists of exons and introns). ExonPCR designs k pairs of primers uniformly covering the cDNA, k is equal to the cDNA length/an average exon length, i.e., the number of equal length fragments which may contain no or any numbers of exons. Each of the fragments is then categorized into a region of (E) no splice site, (I) splice site, or (U) unknown in the first round. Only I and U types of fragments are subject to next round(s) of divisions and categorization (p175, paragraphed 1 and 2 on the right column). Therefore, k is not a number of final predicted exons in the cDNA. Xu merely splices the cDNA, then the I and U types of fragments, to **identify** exon boundaries on an one-by-one basis. In short, the simultaneously designed primers in Xu are based upon equal length fragments rather than the final predicted exons as in the present invention. Moreover, the simultaneously designed primers in Xu are tools for locating the exon boundaries rather than the products derived from the final predicted exons as in the present invention. Accordingly, Xu does not use each of the final predicted exons as a

template to design one corresponding primer pair thereby providing a plurality of primer pairs simultaneously

Secondly, the Examiner relied upon the "common knowledge and common sense" of one skilled in the art to the motivation for combining the teachings in Vijg and Xu did not fulfill the agency's obligation to cite references to support its conclusions. Instead, the Examiner must provide the specific teaching of such a combination on the record to allow accountability.

> *To establish a prima facie case of obviousness, the Board must, inter alia, show "some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). "The motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases the nature of the problem to be solved." Kotzab, 217 F.3d at 1370, 55 USPQ2d at 1317. .... Recently, in In re Lee, 277 F.3d 1338, 61 USPQ2d 1430 (Fed. Cir. 2002), we held that the Board's reliance on "common knowledge and common sense" did not fulfill the agency's obligation to cite references to support its conclusions. Id. at 1344, 61 USPQ2d at 1434. Instead, the Board must document its reasoning on the record to allow accountability. Id. at 1345, 61 USPQ2d at 1435.*

See In re Thrift, 298 F.3d 1357.

Thirdly, the Examiner fails to specify how to combine the predicted exons from Xu with the primer designing or selection method of Vijg. There are more than one way to combine the two processes. For example, using only the predicted exons from the first to third rounds of experiments in Xu to extract primers according to the method in Vijg. Under this scenario, only a limited number (rather than all) of predicted exons contained in the corresponding genomic DNA are designed. A person of ordinary skill in the art could not make a primer design system as claimed by the Applicants based on the above prior teachings except by using Applicants' invention as a blueprint. Applicants will point out that a rejection based on hindsight knowledge of the invention at issue is improper.

Finally, the Examiner relied upon the Generator system in Harris for the motivation to combine different application tools into one program. However, the reference fails to provide any motivation for combining the programs in Vijg and Xu in that it does not provide any specificity for combining the teachings in Vijg and Xu as discussed. Generator only generally "provides an intuitive way to identify the significant regions such as probable exons (abstract), and can call a primer selection program Primer3 (p760, sixth paragraph). It lacks all specificity regarding how to combine the predicted exons from Xu with the primer designing or selection method of Vijg. There is simply no statement and figures in Harris regarding the interaction between exon prediction in a cDNA and the primers extracted from exons which are derived from at least one genomic DNA of in Vijg. As mentioned, there exists more than one way to combine the two processes. As such, Harris fails to compensate for the deficiencies in the teachings of Vijg and Xu.

Even if, arguendo, a person of ordinary skill were motivated to combine the teachings and programs in Vijg and Xu as specified by the Examiner, such combined teachings would still fall short in fully meeting the Applicants' claimed invention as set forth in claim 1 since, as

discussed, there are no teachings of using each of the predicted exons as a template to design one corresponding primer pair thereby providing a plurality of primer pairs simultaneously in Vijg, Xu, or Harris.

As such, the references or their combinations fall far short of anticipating or even rendering obvious every feature of the present invention as now claimed. The present invention as now claimed is distinguishable and thereby allowable over the rejections raised in the Office Action. The withdrawal of the outstanding prior art rejections is in order, and is respectfully solicited.

It is respectfully submitted that the cited references do not teach or suggest each and every element of the applicants' invention as now set forth in other independent claims 1, 7, 30 reciting the same novel feature. Accordingly, the withdrawal of the outstanding rejections under 35 U.S.C. §103 is in order, and is respectfully solicited.

In view of all the above, clear and distinct differences as discussed exist between the present invention as now claimed and the prior art references upon which the rejections in the Office Action rely, Applicants respectfully contend that the prior art references cannot anticipate the present invention or render the present invention obvious. Rather, the present invention as a whole is distinguishable, and thereby allowable over the prior art.

Favorable reconsideration of this application as amended is respectfully solicited. Should there be any outstanding issues requiring discussion that would further the prosecution and allowance of the above-captioned application, the Examiner is invited to contact the Applicants' undersigned representative at the address and phone number indicated below.

Respectfully submitted,

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Marked-up Version of Amended Claims

1. A primer design system, comprising:

means for selecting at least one genomic DNA nucleotide sequence from a database including a plurality of DNA nucleotide sequences;

means for predicting a plurality of exons of said selected DNA nucleotide and for storing positions of the predicted exons;

means for [simultaneously designing a plurality of primer pairs by] using each of the predicted exons as a template to design one corresponding primer pair for each of the predicted exons and for designing corresponding primer pairs for the predicted exons simultaneously; and

means for automatically collating said plurality of primer pairs with said predicted exons and the DNA nucleotide sequence.

30. A method for designing primers, comprising the steps of:

selecting at least one DNA nucleotide sequence from a genomic DNA database;

predicting a plurality of exons of said selected DNA nucleotide;

[simultaneously designing a plurality of primer pairs by] using each of the predicted exons as a template to design one corresponding primer pair for each of the predicted exons and for designing corresponding primer pairs for the predicted exons simultaneously; and

automatically collating said plurality of primer pairs with said predicted exons and the DNA nucleotide sequence.

34. A primer design system, comprising:

means for selecting at least one genomic DNA nucleotide sequence from a database including a plurality of DNA nucleotide sequences;

means for predicting a plurality of exons of said selected DNA nucleotide and for storing positions of the predicted exons;

means for [designing a plurality of primer pairs by] using each of the predicted exons as a template to design one corresponding primer pair for each of the predicted exons and for designing corresponding primer pairs for the predicted exons simultaneously; and

means for evaluating specificity of each designed primer or each designed primer pair.

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running the necessary programs was used for each of the patterns.

Pttern I

Only primer designing was carried out. Pattern I involved running a process for ~~extracting~~ designing a pair of partial sequences, which is preferably predicted and screened, from the predetermined template DNA sequence A1 based on primer design software corresponding to the partial sequence ~~extraction~~ designing processors ~~403~~ 403-415 in Fig. 4. The partial sequence ~~extraction~~ designing conditions were as follows.

(1) base length: 20 to 28 bps;

(2) GC content: 50 to 60%;

(3) Tm: 50 to 80°C; |Tm|: below 20°C; and

(4) located as close as possible to the 5' end or 3' end.

Pattern II

For pattern II, exons were screened, and primers were then designed. For pattern II, exons were screened based on selected conditions from previously prepared exon database 307, then the template DNA sequence A1 (i.e., a screend exon) was transferred through the input 401 to the partial sequence ~~extraction~~ designing processors ~~403, and~~ 403-415 in Fig 4 such that the process for ~~extracting~~ designing partial sequences was run based on primer design software ~~corresponding to the partial sequence extraction processor 403~~. The exon screening conditions are given

below. The partial sequence ~~extraction~~ designing conditions were the same as for pattern I.

(1) exon length: 300 bps or less

(2) exons predicted by an exon predicting program

(3) found in EST database, and expression confirmed

(4) unknown function (not found in protein database)

(5) SNP potential (variation in EST database)

Pattern III

After the exon prediction, exons were screened, and primers were then designed. For pattern III, exons were predicted using software corresponding to the exon predicting program 304 from genomic DNA sequences 303, the output exon sequences 305 were compiled into a database 307 through a sequence input interface 306, exons were screened in the exon database 307 on the basis of the set conditions, then the template DNA sequence A1 (i.e., a predicted then screened exon) was transferred through the input 401 to the partial sequence ~~extraction~~ designing processors 403-415 in Fig. 4 such that ~~403, and~~ the process for ~~extracting~~ designing partial sequences was run by primer design software ~~corresponding to the partial sequence extraction processor 403~~. The exon screening conditions were the same as for pattern II. The partial sequence extraction conditions were the same as for pattern I.